

Cardiac abnormalities in chronic progressive external ophthalmoplegia

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This report describes heart disease in a 32-year-old man with the syndrome of chronic progressive external ophthalmoplegia (CPEO). The surface electrocardiogram showed first degree AV block and left bundle-branch block and there was HV prolongation on the His bundle electrogram. Endomyocardial biopsy showed the changes of hypertrophy on light microscopy, and on electron microscopy there were increased numbers of mitochondria which appeared structurally normal. A permanent demand pacemaker was inserted because these patients are prone to develop complete heart block.

Chronic progressive external ophthalmoplegia (CPEO) may be associated with pigmentary degeneration of the retina, ataxia, facial and limb weakness, and abnormalities of cardiac conduction which predispose to sudden premature death (Kearns, 1965; Drachman, 1968). Patients with complete heart block have been treated with permanent pacemakers (Ross *et al.*, 1969; Uppal, 1973). The most striking pathological findings in CPEO have been accumulation of abnormal mitochondria and considerable deposition of glycogen granules in skeletal and ocular muscle (Morgan-Hughes and Mair, 1973). In this case study we used His bundle recordings in assessing abnormal conduction in a patient with CPEO. The myocardial morphological changes were also studied by biopsy of endomyocardial tissue.

Case report

A 32-year-old man was referred because of his abnormal electrocardiogram. He had been known as 'Sleepy' from the age of 5 years because of bilateral ptosis. Impairment of voluntary eye movement began in adolescence, but this did not affect his physical activities. Throughout his adult life he had had recurrent corneal ulceration and had noticed some change in his facial appearance. There was no diplopia, loss of visual acuity, limb or girdle weakness, ataxia, or bulbar symptoms. Since July 1974 he had had six episodes of giddiness which were of sudden onset and from which he made a spontaneous recovery over one hour. There was no palpitation, chest pain, breathlessness, or loss of consciousness. When seen the heart rate was 80 per minute, regular, and the blood pressure was 130/80 mmHg (17.3/10.6 kPa). The second

heart sound was widely split and varied normally with respiration, and he had a soft systolic murmur at the left sternal edge. General examination was otherwise normal. He was of normal intelligence. He had bilateral ptosis, a divergent squint, and there was a severe and slightly asymmetrical weakness of voluntary and reflex eye movements. The pupillary size and responses were normal. His visual fields and acuity were normal. There was a small right corneal ulcer. His fundi showed a peripheral pigmentary abnormality but the optic discs were normal. He had an asymmetrical facial weakness of lower motor neurone type but his jaw and lingual movements were normal. Palatal and pharyngeal sensation was normal but his pharyngeal reflexes were reduced. There was no muscle wasting or tenderness. He had weakness of neck movements and of all proximal shoulder girdle muscles with normal distal power in the limbs. There was no weakness of the pelvic girdle or lower limbs. The tone was normal and his tendon reflexes were reduced in the upper limbs with normal lower limb tendon reflexes and normal plantar responses. His left arm showed slight incoordination of rapidly alternating movements. His gait was normal. There were no sensory abnormalities.

Investigations

Creatine phosphokinase, aldolase, isocitrate dehydrogenase, gammaglutamyl transpeptidase, lactic dehydrogenase, aspartate transaminase, potassium, calcium creatine, urea, and electrolyte levels in the blood were normal. Haematological investigations included haemoglobin, white cell count, and ESR, all of which were normal. Serum thyroxine was normal. X-ray examinations of the skull, chest, and lumbosacral spine were normal.

Nerve conduction studies showed normal conduction in the left lateral popliteal nerve. Electromyography

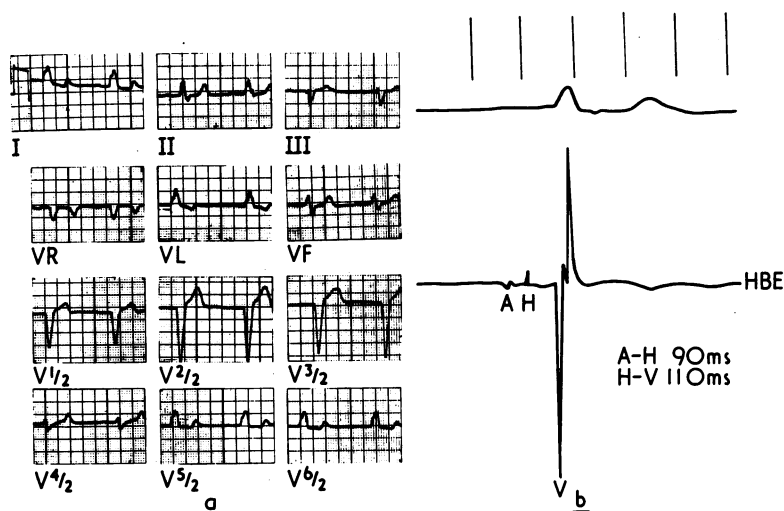


FIG. 1 (a) Electrocardiogram showing first degree atrioventricular block and left bundle-branch block. (b) His bundle electrocardiogram showing prolonged HV interval. Time lines at 200 ms.

showed a normal left tibialis anterior muscle, but there was an excessive number of small, short-duration polyphasic units in the left biceps muscle. Biopsy of tissue from the left triceps muscle showed some variation in fibre size and about 5 per cent of fibres showed mitochondrial accumulations. On electron microscopy the mitochondria were seen to contain paracrystalline inclusions and vacuoles and there was increased glycogen deposition around the mitochondria and between the myofibrils. The electroencephalogram was normal.

The electrocardiogram showed first degree atrioventricular block (PR interval 0.22 s) and left bundle-branch block (Fig. 1a). The echocardiogram was normal. At cardiac catheterization all pressures were normal, including the left ventricular end-diastolic pressure, and there were no valvular abnormalities. The left ventriculogram was normal. His bundle recordings were obtained with a bipolar catheter positioned as previously described (Scherlag *et al.*, 1969). A simultaneous electrocardiogram and His bundle tracing are shown in Fig. 1b. During sinus rhythm the AH interval was 90 ms (normal range 80–190 ms) and the HV interval 110 ms (normal range 35–55 ms). Atrial pacing produced a sequential increase in the AH interval without altering the HV interval.

Right and left ventricular tissue for biopsy was obtained by the transfemoral percutaneous route. Light microscopy of the right ventricular specimen showed interstitial fibrosis with hypertrophy of the myocardial fibres and thickening of the endocardium to 40 μ (normal range up to 20 μ). Similar changes were seen in the left ventricular specimen with more distinct thickening of the endocardium. Electron microscopy showed regular arrangements of the myocardial fibrils with mitochondrial accumulation and increased glycogen deposition (Fig. 2). The mitochondria were structurally

normal and the changes were indistinguishable from those of ordinary hypertrophy.

The patient gave his consent to the investigations, the nature of which was fully explained to him beforehand.

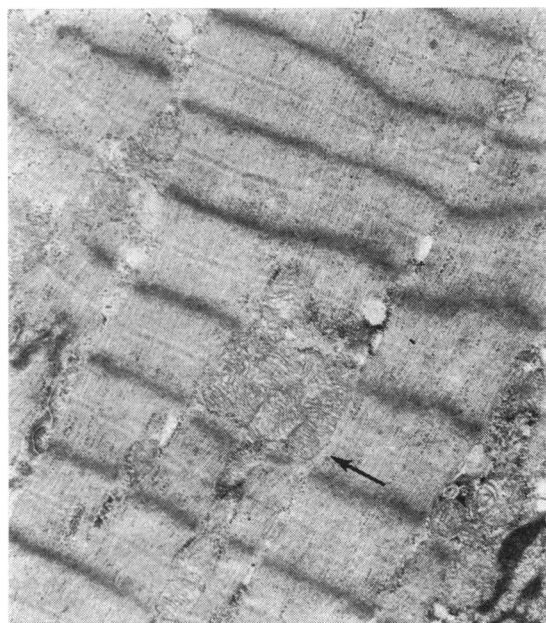


FIG. 2 Right ventricular biopsy. Increased numbers of mitochondria which appear morphologically normal (arrowed).

Management

A permanent demand pacemaker was inserted as a prophylactic measure.

Discussion

The variety of clinical associations of chronic progressive external ophthalmoplegia has led to uncertainty about the nature of the disease. The neurological component may be a primary myopathy (Kiloh and Nevin, 1951) or a denervation atrophy (Drachman *et al.*, 1969) or may represent the clinical manifestations of a single metabolic defect (Morgan-Hughes and Mair, 1973). No constant aetiological factor has been found. The nature of the involvement of the heart is equally uncertain. It has been called a cardiomyopathy (Uppal, 1973) but no histological changes have been described to support this contention. Postmortem studies have not been helpful (Jager *et al.*, 1960; Kearns, 1965).

The technique of percutaneous biopsy of the right and left ventricles of the heart is firmly established (Konno, Sekiguchi, and Sakakibara, 1971; Richardson, 1974). The endomyocardial biopsy in this patient showed changes not previously described in CPEO. The histological feature (regular arrangement of fibrils with mitochondrial accumulation and increased glycogen deposition) were of hypertrophy—an unexpected finding in this normotensive patient with no evidence of valvular heart disease. This finding may be significant in view of the changes found in ocular and skeletal muscle of this and other patients (Morgan-Hughes and Mair, 1973), which suggest that the mitochondria are intimately involved in the disease process. Cardiac involvement in other forms of muscular dystrophy includes abnormalities of the myocardium and conduction tissue. The myocardial involvement may lead to severe heart failure, as in the pseudohypertrophic type of muscular dystrophy and in Friedreich's ataxia (Taylor, 1974). The normal left ventricular pressures and ventriculogram and the abnormal intracardiac conduction in this patient emphasize that the cardiac involvement in CPEO is different as the conducting system bears the brunt of the disease process. Other manifestations of this cardiomyopathy may appear if prolonged survival occurs with pacing.

Patients with bifascicular block caused by chronic sclerodegenerative disease of the conducting tissue, such as right bundle-branch block and left anterior hemiblock, are known to develop complete heart block, the estimated risk being 6 per cent per year of follow-up (Kulbertus, 1973). In these patients this is not thought to be sufficient indication

for the insertion of a prophylactic pacemaker. When such patients are further assessed by His bundle recordings a prolonged HV time, indicating delayed conduction in the His Purkinje system, may be found. To date, however, the value of such abnormal recordings in predicting the onset of complete heart block has not been established (De Pasquale and Bruno, 1974).

The conduction disturbance in CPEO seems to behave differently. These patients appear to progress from incomplete to complete heart block relatively often. Complete heart block has been preceded by right bundle-branch block and left anterior hemiblock in at least 5 cases and by isolated left bundle-branch block in one case (Drachman, 1968). In the only previously reported case of His bundle studies in CPEO (Morris *et al.*, 1972) the patient had a prolonged HV time and developed second degree AV block (Mobitz type II) when given atropine. Subsequently, episodes of complete heart block occurred. In our patient the HV time was very prolonged and the surface electrocardiogram showed first degree atrioventricular block and left bundle-branch block (Fig. 1a). Though not an indication for pacing in sclerodegenerative disease of the conducting system (Scheinman, Weiss, and Kunkel, 1973), in the unusual group of patients with CPEO and conduction defects the prolonged HV time may be important in deciding to implant a permanent pacemaker even in the absence of symptoms.

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